

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number  
**WO 01/05388 A2**

- (51) International Patent Classification<sup>7</sup>: A61K 31/00      (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
- (21) International Application Number: PCT/JP00/04696
- (22) International Filing Date: 13 July 2000 (13.07.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/143,627                  14 July 1999 (14.07.1999) US
- (71) Applicant: R-TECH UENO, LTD. [JP/JP]; 4-8, Koraibashi 2-chome, Chuo-ku, Osaka-shi, Osaka 541-0043 (JP).
- (72) Inventor: UENO, Ryuji; 11025 Stanmore Drive, Potomac, Montgomery, MD 20854 (US).
- (74) Agents: AOYAMA, Tamotsu et al.; Aoyama & Partners, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540-0001 (JP).

Published:

- Without international search report and to be republished upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/05388 A2

(54) Title: COMPOSITION FOR TREATMENT OF EXTERNAL SECRETION DISORDERS

(57) Abstract: Disclosed is a composition for treatment of external secretion disorders comprising, as an active ingredient a fatty acid derivative. The composition of the present invention is useful for treatment of at least one condition selected from hypolacrimation including disorder of basal tear secretion, dry-eye syndrome, hyposalivation and dry-mouth syndrome.

DESCRIPTION  
COMPOSITION FOR TREATMENT OF EXTERNAL  
SECRETION DISORDERS

5      TECHNICAL FIELD

The present invention relates to a composition for treatment of external secretion disorders, particularly, to a composition for treatment of hypolacrimation including dry-eye syndrome and hyposalivation including dry-mouth syndrome. The present invention also relates to a method for treatment of external secretion disorders and use of a certain compound for manufacturing a pharmaceutical composition for treatment of external secretion disorders.

15      BACKGROUND ART

External secretions are discharges that are discharged directly from the exocrine glandular cells or through the excretory ducts or the like onto the body surface or into a lumen. Tear and saliva are the typical external secretions and secretions from the nasal or the respiratory tract mucosa, secretions from the stomach or the intestine, discharges from the vagina, perspiration, etc are also included. Conditions resulting from external secretion disorders include dryness of various parts of the body such as "dry-eye syndrome" (xerophthalmia), "dry-mouth syndrome"(xerostomia), "dry-nose

syndrome"(xeromycteria), "dry-skin syndrome"(xeroderma), and "dry-vagina syndrome"(symptom of vaginal dryness); and chronic pancreatitis, chronic gastritis, and chronic bronchitis due to depression of the external secretion.

5            "Sjögren's syndrome", an autoimmune disease, is one of the variety of known and unknown etiologic factors which may responsible for external secretion disorders. Sjögren's syndrome is characterized by dryness condition due to infiltration of inflammatory cells into the acinus of  
10          the exocrine gland and around the excretory duct, which results in destruction and atrophy of the acinus and the epithelial cells of the duct. Typical symptoms include eye and mouth dryness, as well as dryness of skin, nose, throat, bronchia, vulva, and vagina. For example, dryness of the  
15          respiratory tract may induce infections in the lung and sometimes may cause serious disorders such as pneumonia that may lead to death. The other major etiology is aging. Although the external secretion disorders may cause serious diseases as mentioned above, merely symptomatic  
20          treatment methods such as artificial hydration have been available for the disorders so far. Therefore, development of a fundamental treatment to improve the depressed external secretion has been desired.

One of the diseases caused by the external  
25          secretion disorders, and which has been a current keen

interest in the medical and pharmaceutical field, is hypolacrimation including dry-eye syndrome.

Dry-eye syndrome is defined as a condition with decrease or change in quality of tear irrespective of the presence or absence of corneal and conjunctival lesion (Yamada et al., GANKI 43, 1289-1293(1992)). It include dry-eye conditions found in the patients of hypolacrimation, alacrima, xerophthalmia, Sjögren's syndrome, keratoconjunctivitis sicca, Stevens-Johnson syndrome, ocular pemphigoid, blepharitis marginal, and diabetes, etc.; post-cataract surgery dry eye; allergic conjunctivitis-associated dry eye; and age-related dry-eye syndrome. Further, dry-eye also includes the conditions found in hypolacrimation patients induced by long time visual display terminal (VDT) operations, room dryness due to air-conditioning and the like.

There are various etiologies of the dry-eye syndrome, including the above described and that have unidentified. However, at present, only palliative treatments for the dry-eye syndrome including administering an artificial tear solution to increase the quantity of tear retained within the conjunctival sac thereby relieve the subjective symptoms or protecting the eyes from dryness have been available. It has been desired to provide compositions which is capable of bringing satisfactory

treatment, including improvement of hypolacrimation.

The tear secretion is classified into basal tear secretion and reflex tear secretion. Basal tear secretion is that under ordinary conditions with the eyelid open, and is considered being mainly from the accessory lacrimal glands e.g. Kraus gland and Wolfring gland. On the other hand, reflux tear secretion is tear secretion in response to some stimulation in the keratoconjunctival surface, nasal mucosa, or the like, or that accompanied with mental changes such as grief or joy. It is considered to be from the main lacrimal gland. Considering the symptoms of the dry-eye syndrome, improvement of the decreased basal tear secretion, i.e. tear secretion under ordinary conditions with the eyelid open, is particularly important.

Further, the diseases caused by external secretion disorders also include hyposalivation, and it may be sometimes accompanied by dry-mouth syndrome(xerostomia). In dry-mouth patients, the decreased amount of saliva secretion causes dryness of the lip and oral cavity and may induce thirst feeling, xerosis of tunica mucosa oris, urtication, dysmaesesis, and dyspepsia. Also, in the patients with dry-mouth syndrome, foods are likely to remain inside the mouth and may result in dental caries.

There are a variety of etiologic factors that are

responsible for the dry-mouth syndrome. For example, systemic factors include febrile disease, dehydration, endocrinopathy (myxedema, Basedow's disease, diabetes insipidus, etc.) metabolic disorders (diabetes, uremia, liver 5 cirrhosis, etc.) deficiency of Vitamin-A, B, autoimmune disease (Sjögren's syndrome, progressive scleroderma, etc.) anemia, bleeding, aging, various medicaments (sedatives, parasympatholytic drugs, antihistamines, etc.). Local factors include sialadenitis, atrophy of salivary gland, 10 sequela of radio therapy, and malformation (ectodermal dysplasia, etc.)

As described above, there are a variety of known and unknown etiologic factors responsible for the dry-mouth syndrome. However, at present, only palliative treatments 15 for the dry-mouth syndrome such as drinking liquid all day long little by little, chewing gum or the like, and using artificial saliva have been available. It has been desired to provide a composition which is capable of bringing fundamental treatment such that to improve the decreased 20 saliva secretion.

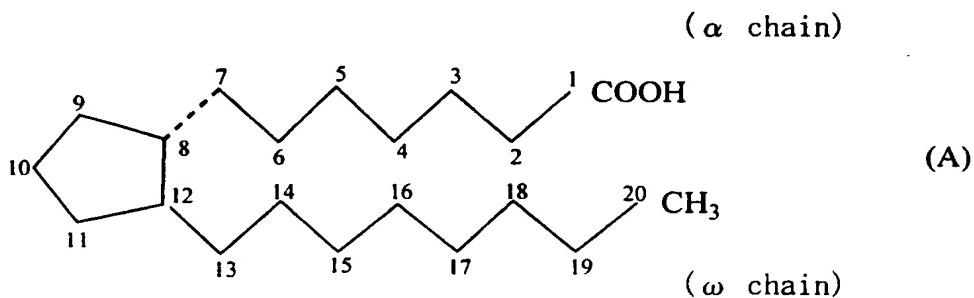
Generally, a healthy normal person discharges 1 to 1.5 litter of saliva a day through a pair of left and right major salivary glands (including parotid gland, submandibular gland, and sublingual gland) and minor 25 salivary glands (including labial glands, lingual glands,

palatine glands, and buccal glands). Saliva is discharged in response to a stimulant, which may harm body to dilute the same or to maintain the physiological pH value, as well as helping mastication and deglutition of foods. Further, 5 saliva dissolves foods thereby makes a person taste them and helps him smoothly utter words by keeping a wet state inside the mouth. There are two types of saliva: one is the continuous type that keeps on discharging a small amount without a particular stimulant and the other is the reflective 10 type that is discharged in response to stimulation by food, gnatho-movement, taste and the like. In any case, saliva secretion is one of the essential physiological functions and hence improving the decreased saliva secretion is particularly important in treating the dry-mouth syndrome.

15 In the past, some of fatty acids had been rated as essential, and enough amount of them were required to be taken from the nutrient point of view. Recently, bioactivities of a variety of fatty acids have been studied and the activities of linoleic acid, arachidonic acid,  $\alpha$ -linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) have attracted the attention. Linoleic acid is converted through di-homo- $\gamma$ -linolenic acid to arachidonic acid;  $\alpha$ -linolenic acid is converted through eicosapentaenoic acid(EPA) to docosahexaenoic acid 20 (DHA); di-homo- $\gamma$  -linolenic acid is converted into type 1 25

prostaglandin (PG<sub>1</sub>), arachidonic acid is converted into type 2 prostaglandin (PG<sub>2</sub>) or type 4 leukotriene (LT<sub>4</sub>), and eicosapentaenoic acid is converted into type 3 prostaglandin or type 5 leukotriene (LT<sub>5</sub>) in vivo  
5 respectively.

Prostaglandins (hereinafter, referred to as PG(s)) are members of class of organic carboxylic acids, which are contained in tissues or organs of human or most other mammalian, and exhibit a wide range of physiological activity. PGs found in nature (primary PGs) generally have 10 a prostanoic acid skeleton as shown in the formula (A):



On the other hand, some of synthetic analogues have a modified skeleton. The primary PGs are classified 15 to PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs, PGHs, PGIs and PGJs according to the structure of the five-membered ring moiety, and further classified into the following three types by the number and position of the unsaturated bond at the carbon chain moiety:

20 subscript 1: 13,14-unsaturated-15-OH

subscript 2: 5,6- and 13,14-diunsaturated-15-OH

subscript 3: 5,6-, 13,14-, and 17,18-triunsaturated-15-OH.

Further, the PGFs are classified, according to the configuration of the hydroxyl group at the 9-position, into  $\alpha$  type (the hydroxyl group is of an  $\alpha$ -configuration) and  $\beta$  type (the hydroxyl group is of a  $\beta$ -configuration).

In addition, some 15-keto (i.e. having an oxo group at position 15 in place of the hydroxy group) prostaglandins and 13,14-dihydro-15-keto-prostaglandins are known as substances naturally produced by enzymatic actions during in vivo metabolism of primary PGs. 15-keto PGs have been disclosed in, for example, EP-A-0281239 (corresponds to JP-A-104040/89), EP-A-0281480 (corresponds to JP-A-52753/89), EP-A-0289349 (corresponds to JP-A-151552/89), EP-A-0453127 (JP-A-15 58992/95) and EP-A-0690049 (corresponds to JP-A-48665/96). These cited references are herein incorporated by reference.

For example, when a primary type PG such as PGE<sub>2</sub> or PGF<sub>2</sub> $\alpha$  which is a fatty acid derivative is instilled to the eyes at a stimulating amount which induces conjunctival hyperemia, lacrimation will occur simultaneously with the hyperemia. However, at an amount as low as that does not induce any conjunctival hyperemia, it is not known about the effect of the fatty acid derivatives including PGs on the tear secretion, basal tear secretion which is not affected by

a stimulant, nor saliva secretion.

## SUMMARY OF THE INVENTION

An object of the present invention is to provide a composition and method for treatment of external secretion disorders, especially those useful for treatment of at least one condition selected from hypolacrimation, dry-eye syndrome, hyposalivation and dry-mouth syndrome.

The present inventor found that at an amount as low as that does not induce any conjunctival hyperemia, a fatty acid derivative may improve hypolacrimation, improve basal tear secretion which is not affected by a stimulant, and improve the dry-eye conditions. In addition, the inventor also found that the fatty acid derivative might also improve hyposalivation, and improve dry-mouth conditions.

Therefore, the present invention provides a composition for treatment of external secretion disorders, especially, for treatment of hypolacrimation, dry-eye syndrome, hyposalivation or dry-mouth syndrome, which comprises a fatty acid derivative as an active ingredient.

The present invention also provides a method for treatment of external secretion disorders, which comprises administering an effective amount of a fatty acid to a subject in need of said treatment.

The present invention further provide use of a fatty acid derivative for producing a pharmaceutical

composition for treatment of external disorders.

According to this invention, the term "fatty acid" includes not only the above mentioned linoleic acid, di-homo- $\gamma$ -linolenic acid, arachidonic acid,  $\alpha$ -linolenic acid, 5 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), but also a compound comprising at least one carboxylic acid moiety irrespective to presence or absence of double bonds, a cyclic group or a substitute group, the number of the carbon atoms, position or number of the 10 double bonds, or a modification on the chain. In addition, the fatty acid derivatives include not only the fatty acids as above but also prostaglandin like compounds which include PG<sub>s</sub> derived from said fatty acids, leukotriene like compounds, thromboxanes, hydroxyeicosatetraenoic acids, 15 hydroperoxyeicosatetraenoic acids or their derivatives.

Furthermore, in the present invention, the fatty acid derivatives also include the compound which have at least -COOH or -CH<sub>2</sub>OH or the functional derivatives(salts, esters, ethers, amides or the like) thereof at the terminal carbon 20 atom, irrespective to presence or absence of double bonds, a cyclic group or a substitute group, the number of the carbon atoms, position or number of the double bonds, or a modification on the chain.

According to the present invention, the term 25 "prostaglandin like compound" (hereinafter, referred as "PG

like compound") includes any of derivatives or substituted derivatives of a compound having the prostanoic acid basic structure irrespective to the configuration of the 5-membered ring, number of double bonds in the  $\alpha$  or  $\omega$  chain, presence 5 or absence of hydroxy and oxo groups or any other substituent, or any other modification. Since the PG like compound of the present invention may have an activity as an agonist for PG-receptor such as EP, FP, IP TP or DP receptor, the "PG like compound" of the present invention 10 may include each compound having PG-receptor agonistic activity irrespective to their structure.

The nomenclature of the PG like compounds used herein is based on the numbering system of the prostanoic acid represented in the above formula (A).

15 The formula (A) shows a basic skeleton of the C-20, but the PG like compounds in the present invention are not limited to those having the same number of carbon atoms. In the formula (A), the numbering of the carbon atoms which constitute the basic skeleton of the PG 20 compounds starts at the carboxylic acid (numbered 1), and carbon atoms in the  $\alpha$ -chain are numbered 2 to 7 towards the five-membered ring, those in the ring are 8 to 12, and those in the  $\omega$ -chain are 13 to 20. When the number of carbon atoms is decreased in the  $\alpha$ -chain, the number is 25 deleted in the order starting from position 2; and when the

number of carbon atoms is increased in the  $\alpha$ -chain, compounds are named as substitution compounds having respective substituents at position 2 in place of carboxy group (C-1). Similarly, when the number of carbon atoms is 5 decreased in the  $\omega$ -chain, the number is deleted in the order starting from position 20; and when the number of carbon atoms is increased in the  $\omega$ -chain, the carbon atoms over position 20 are named as substituents. Stereochemistry of the compounds is the same as that of 10 the above formula (A) unless otherwise specified.

In general, each of PGD, PGE and PGF represents a PG compound having hydroxy groups at positions 9 and/or 11, but in the present specification, they also include those having substituents other than the 15 hydroxy group at positions 9 and/or 11. Such compounds are referred to as 9-dehydroxy-9-substituted-PG compounds or 11-dehydroxy-11-substituted-PG compounds. A PG compound having hydrogen in place of the hydroxy group is simply named as 9- or 11-dehydroxy compound.

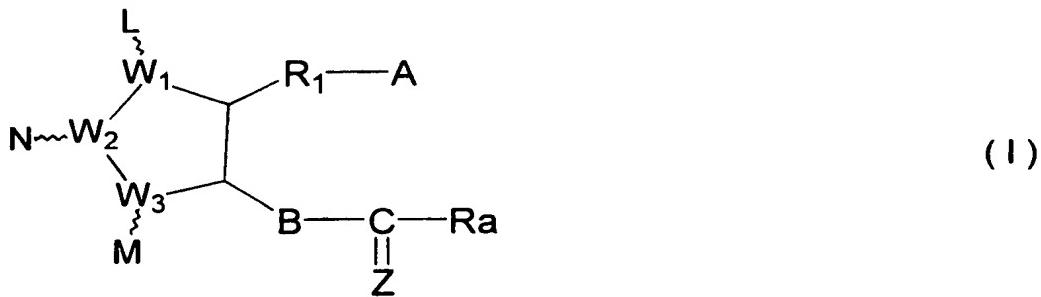
As stated above, the nomenclature of the PG like compounds is based on the prostanoic acid skeleton. However, in case the compound has a similar partial construction as a prostaglandin, the abbreviation of "PG" may be used. Thus, a PG compound of which  $\alpha$ -chain is 25 extended by two carbon atoms; that is, having 9 carbon

atoms in the  $\alpha$ -chain is named as 2-decarboxy-2-(2-carboxyethyl)-PG compound. Similarly, a PG compound having 11 carbon atoms in the  $\alpha$ -chain is named as 2-decarboxy-2-(4-carboxybutyl)-PG compound, and a PG 5 compound having 10 carbon atoms in the  $\omega$ -chain is named as 20-ethyl-PG compound. These compounds, however, may also be named according to the IUPAC nomenclatures.

The PG like compounds used in the present invention may include any of PG derivatives. Accordingly, 10 for example, a PG<sub>1</sub> compound having a double bond at 13-14 position and a hydroxy group at 15-position, a PG<sub>2</sub> compound having another double bond at 5-6 position, a PG<sub>3</sub> compound having further double bond at 17-18 position, a 15-keto-PG compound having an oxo group in place of the 15 hydroxy group at the 15-position, a 15-dehydroxy-PG compound having a hydrogen atom in place of the hydroxy group at the 15-position, or either 13,14-dihydro-PG compound wherein the double bond at 13-14 position is single bond, or 13,14-didehydro-PG compound wherein the 15 double bond at the 13-14 position is triple bond. Moreover, examples of substituted compounds and derivatives include 20 a compound wherein the terminal carboxyl group in the  $\alpha$ -chain of the above described compound is esterified, a physiologically acceptable salt thereof, a compound 25 wherein the number of carbon atoms in the  $\alpha$ - or  $\omega$ -chain is

decreased or increased, a compound having side chains (e.g., 1 to 3 carbon atoms) on  $\alpha$ - or  $\omega$ -chains, a compound having substituent(s) such as hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, and oxo, or double bond(s) on the five-membered ring, a compound having substituent(s), such as halogen, oxo, aryl and heterocyclic on the  $\alpha$ -chain, a compound having substituents such as halogen, oxo, hydroxy, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic and heterocyclic-oxy on the  $\omega$ -chain, and a compound having substituent such as lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic and heterocyclic-oxy at the terminal of the  $\omega$ -chain of which is shorter than that of normal prostanoic acid.

A preferred compound used in the present invention is represented by the formula (I):



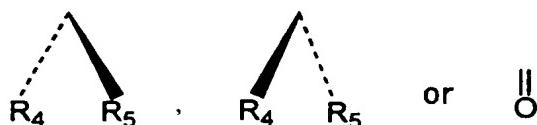
wherein  $W_1$ ,  $W_2$  and  $W_3$  are carbon or oxygen atoms, L, M and N are hydrogen, hydroxy, halogen, lower

alkyl, hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is -CH<sub>2</sub>OH, -COCH<sub>2</sub>OH, -COOH or its functional derivative;

B is single bond, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -C≡C-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH=CH-, -C≡C-CH<sub>2</sub>-, or -CH<sub>2</sub>-C≡C-;

Z is



10

wherein R<sub>4</sub> and R<sub>5</sub> are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R<sub>4</sub> and R<sub>5</sub> are not hydroxy and lower alkoxy at the same time;

15

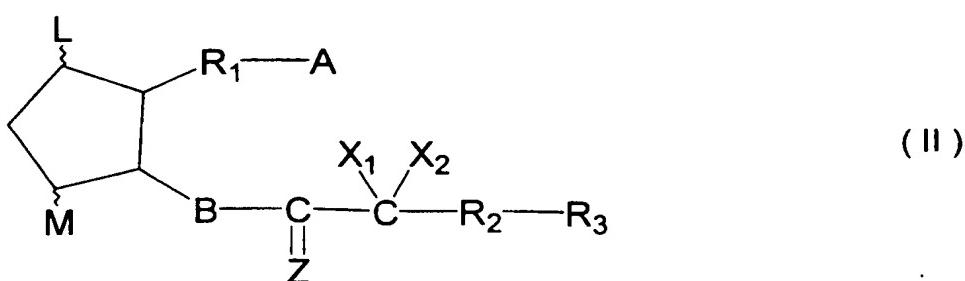
R<sub>1</sub> is a divalent saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkyl, aryl or heterocyclic; and

20

R<sub>a</sub> is a saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic or

heterocyclic-oxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic; heterocyclic-oxy.

A group of particularly preferable compounds among the above described compounds is represented by  
5 the general formula (II):

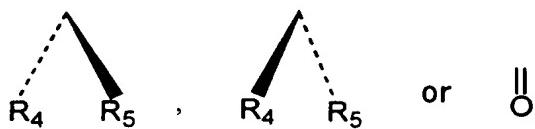


wherein L and M are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the 10 five-membered ring may have at least one double bond;

A is -CH<sub>2</sub>OH, -COCH<sub>2</sub>OH, -COOH or its functional derivative;

B is single bond, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -C≡C-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH=CH-, -C≡C-CH<sub>2</sub>-, or -  
15 CH<sub>2</sub>-C≡C-;

Z is



20 wherein R<sub>4</sub> and R<sub>5</sub> are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl,

wherein R<sub>4</sub> and R<sub>5</sub> are not hydroxy and lower alkoxy at the same time;

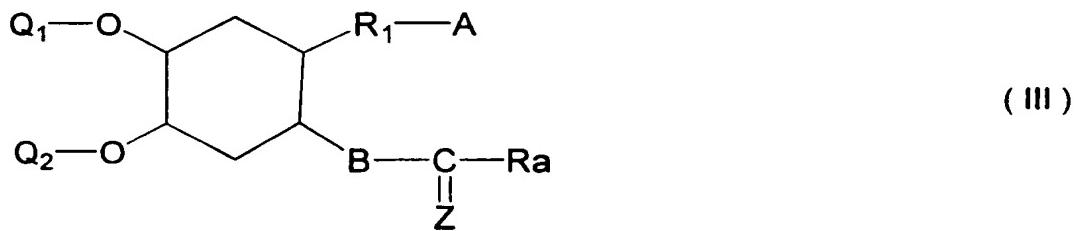
X<sub>1</sub> and X<sub>2</sub> are hydrogen, lower alkyl, or halogen;

R<sub>1</sub> is a divalent saturated or unsaturated lower-medium 5 aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkyl, aryl or heterocyclic;

R<sub>2</sub> is a single bond or lower alkylene; and

R<sub>3</sub> is lower alkyl, lower alkoxy, cyclo(lower)alkyl, 10 cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic or heterocyclic-oxy.

Other preferred compound used in the present invention is represented by the formula (III):



15

wherein Q<sub>1</sub> and Q<sub>2</sub> are hydrogen or lower alkyl, or Q<sub>1</sub> and Q<sub>2</sub> are linked together to form -(CH<sub>2</sub>)<sub>n</sub>- wherein n is 1, 2 or 0, and six-membered ring may have at least one double bond;

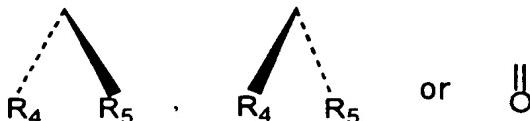
A is -CH<sub>2</sub>OH, -COCH<sub>2</sub>OH, -COOH or its functional derivative;

B is single bond, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -C≡C-, -CH<sub>2</sub>-

$\text{CH}_2\text{-CH}_2\text{-}$ ,  $-\text{CH=CH-CH}_2\text{-}$ ,  $-\text{CH}_2\text{-CH=CH-}$ ,  $-\text{C}\equiv\text{C-CH}_2\text{-}$ , or  $-\text{CH}_2\text{-C}\equiv\text{C-}$ ;

Z is

5



wherein  $R_4$  and  $R_5$  are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein  $R_4$  and  $R_5$  are not hydroxy and lower alkoxy at the same time;

10         $R_1$  is a divalent saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkyl, aryl or heterocyclic;

15         $R_a$  is a saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, hydroxy, alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic or heterocyclic-oxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; 20        heterocyclic; heterocyclic-oxy; and

the six-membered ring may optionally have one or more double bonds and may optionally consist a conjugated system.

25        Among the above described compound (III), a preferable compound is benzene ring type compound in the

six-membered ring.

In the above formula, the term "unsaturated" in the definitions for R<sub>1</sub> and R<sub>a</sub> is intended to include at least one or more double bonds and/or triple bonds that are isolatedly, 5 separately or serially present between carbon atoms of the main and/or side chains. According to the usual nomenclature, an unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two 10 distal positions is represented by denoting both of the positions. Preferred unsaturated bonds are a double bond at position 2 and a double or triple bond at position 5.

The term "lower-medium aliphatic hydrocarbon" means a hydrocarbon having a straight or branched chain of 15 1 to 14 carbon atoms, wherein the side chain has preferably 1 to 3 carbon atoms. The preferred R<sub>1</sub> has 1 to 10, more preferably, 1 to 8 carbon atoms, and the preferred R<sub>a</sub> has 1 to 10, more preferably, 1 to 8 carbon atoms.

The term "halogen" includes fluorine, chlorine, 20 bromine, and iodine.

The term "lower" means a group having 1 to 6 carbon atoms unless otherwise specified.

The term "lower alkyl" means a straight- or branched-chain saturated hydrocarbon group having 1 to 6 25 carbon atoms, for example, methyl, ethyl, propyl, isopropyl,

butyl, isobutyl, t-butyl, pentyl, and hexyl.

The term "lower alkoxy" means a lower alkyl-O- wherein the lower alkyl is as described above.

5 The term "hydroxy(lower)alkyl" means an alkyl as described above, which is substituted by at least one hydroxy group, for example, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, and 1-methyl-1-hydroxyethyl.

10 The term "lower alkanoyloxy" means a group represented by the formula RCO-O-, wherein RCO- is an acyl formed by oxidation of a lower alkyl as described above, for example, acetyl.

15 The term "lower cycloalkyl" means a group formed by cyclization of a lower alkyl group containing 3 or more carbon atoms as described above, for example, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The term "cyclo(lower)alkyloxy" means a group represented by the formula cycloalkyl-O-, wherein cycloalkyl is described above.

20 The term "aryl" includes aromatic hydrocarbon rings (preferably monocyclic groups) which may be substituted, for example, phenyl, tolyl and xylyl. Examples of the substituent in this case include halogen, and halogen substituted lower alkyl group, wherein halogen atom and lower alkyl group are as described above.

25 The term "aryloxy" means a group represented by

the formula ArO-, wherein Ar is an aryl group as described above.

The term "heterocyclic" includes mono- to tri-cyclic, preferably monocyclic heterocyclic group which is 5 to 14, 5 preferably 5 to 10 membered ring having optionally substituted carbon atom and 1 to 4, preferably 1 to 3 of 1 or 2 type of hetero-atoms selected from nitrogen atom, oxygen atom and sulfur atom. Examples of the heterocyclic group include furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, 10 thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furazanyl, pyranyl, pyridyl, pyridazyl, pyrimidyl, pyrazyl, 2-pyrrolinyl, pyrrolidinyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, indolyl, benzothienyl, quinolyl, isoquinolyl, puryl, quinazolinyl, 15 carbazolyl, acridinyl, phenanthridinyl, benzimidazolyl, benzimidazolonyl, benzothiazolyl, phenothiazinyl. Examples of the substituent in this case include halogen, and halogen substituted lower alkyl group, wherein halogen atom and lower alkyl group are as described above.

20 The term "heterocyclic-oxy" means a group represented by the formula HcO-, wherein Hc is a heterocyclic group as described above.

The term "functional derivative" of A includes salts (preferably pharmaceutically acceptable salts), ethers, 25 esters, and amides.

Examples of suitable "pharmaceutically acceptable salts" include nontoxic salts which are commonly used, and salts with inorganic bases, for example, alkali metal salts (sodium salt, potassium salt and the like); 5 alkaline earth metal salts (calcium salt, magnesium salt and the like); ammonium salts; salts with organic bases, for example, amine salts (such as methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, 10 diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)ethane salt, monomethylmonoethanolamine salt, lysine salt, procaine salt, and caffeine salt); basic amino acid salts (such as arginine salt, and lysine salt); tetraalkyl ammonium salts and the like. 15 These salts may be manufactured from, for example, corresponding acids and bases in accordance with a conventional manner or salt exchange.

Examples of the ethers include alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ethyl ether; and medium or higher alkyl ethers such as octyl ether, diethylhexyl ether, lauryl ether and cetyl ether; unsaturated ethers such as oleyl ether and linolenyl ether; 25 lower alkenyl ethers such as vinyl ether, allyl ether; lower

alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy(lower)alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy (lower)alkyl ethers such as methoxymethyl ether and 1-methoxyethyl ether; 5 optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-dimethoxyphenyl ether and benzamidophenyl ether; and aryl(lower)alkyl ethers such as benzyl ether, trityl ether and benzhydryl ether.

10 Examples of the esters include aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, and 1-cyclopropylethyl ester; lower alkenyl esters such as vinyl ester, and allyl ester; lower alkynyl esters such as ethynyl ester, and propynyl ester; hydroxy(lower)alkyl esters such as hydroxyethyl ester; and lower alkoxy(lower)alkyl esters such as methoxymethyl ester, and 1-methoxyethyl ester as well as, for example, optionally substituted aryl esters such 15 as phenyl ester, tosyl ester, t-butylphenyl ester, salicyl ester, 3,4-dimethoxyphenyl ester, and benzamidephenyl ester; and aryl(lower)alkyl esters such as benzyl ester, trityl ester, and benzhydryl ester. An example of amides includes mono- or di-lower alkyl amides such as 20 methylamide, ethylamide, and dimethylamide; aryl amides 25 such as phenyl amide, tosyl amide, t-butylphenyl amide, salicyl amide, 3,4-dimethoxyphenyl amide, and benzamidephenyl amide.

such as anilide, and toluidide; and alkyl or aryl sulfonyl amides such as methylsulfonyl amide, ethylsulfonyl amide, and tolylsulfonyl amide.

Preferred examples of L and M include hydroxy and oxo, and especially, M is hydroxy and L is oxo which provide a 5-membered ring structure of, so called, PGE type.

Preferred examples of A-group include -COOH, and a pharmaceutically acceptable salt, an ester and an amide thereof.

In the formula (I) and (II), B is preferably -CH<sub>2</sub>-CH<sub>2</sub>- which provides the structure of so-called, 13,14-dihydro type.

In the formula (III), B is preferably single bond.

In the formula (I) and (II), Z is preferably =O which provides the structure of so-called keto-type.

In the formula (III), Z is preferably hydroxy.

Preferred examples of X<sub>1</sub> and X<sub>2</sub> are that at least one of them is halogen, more preferably, both of them are halogen, especially, fluorine that provides a structure of, so called 16,16-difluoro type.

Preferred R<sub>1</sub> is a hydrocarbon containing 2-10 carbon atoms, more preferably, 4-8 carbon atoms.

Examples of R<sub>1</sub> include, for example, the following groups:

-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-,  
-CH<sub>2</sub>-CH=CH-CH<sub>2</sub>-,  
-CH<sub>2</sub>-C≡C-CH<sub>2</sub>-.  
-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-,  
5 -CH<sub>2</sub>-CH=CH-CH<sub>2</sub>-CH<sub>2</sub>-,  
-CH<sub>2</sub>-C≡C-CH<sub>2</sub>-CH<sub>2</sub>-,  
-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-,  
-CH<sub>2</sub>-CH=CH-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-,  
-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH=CH-  
10 -CH<sub>2</sub>-C≡C-CH<sub>2</sub>-CH<sub>2</sub>-,  
-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH(CH<sub>3</sub>)-CH<sub>2</sub>-  
-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-,  
-CH<sub>2</sub>-CH=CH-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-,  
-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH=CH-  
15 -CH<sub>2</sub>-C≡C-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-,  
-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH(CH<sub>3</sub>)-CH<sub>2</sub>-.

Preferred Ra is a hydrocarbon containing 1-10 carbon atoms, more preferably, 1-8 carbon atoms and, especially, that having one or two side chains with one carbon atom.

The configuration of the ring and the α- and/or ω chains in the above formula (I) may be the same as or different from that of the primary PGs. However, the present invention also includes a mixture of a compound 25 having a primary type configuration and a compound of a

non-primary type configuration.

An example of the typical compound according to the present invention is 13,14-dihydro-15-keto-16-mono or di-fluoro PGE compound or a derivative thereof.

When a 15-keto-PG compound of the present invention has a saturated bond between positions 13 and 14, the compound may be in the keto-hemiacetal equilibrium by formation of a hemiacetal between hydroxy at position 11 and keto at position 15.

If such tautomeric isomers as above are present, the proportion of both tautomeric isomers varies with the structure of the rest of the molecule or the kind of the substituent present. Sometimes one isomer may predominantly be present in comparison with the other. However, it is to be appreciated that the compounds used in the invention include both isomers. Further, while the compounds used in the invention may be represented by a structure formula or name based on keto-type regardless of the presence or absence of the isomers, it is to be noted that such structure or name does not intend to eliminate the hemiacetal type compound.

In the present invention, any of isomers such as the individual tautomeric isomers, the mixture thereof, or optical isomers, the mixture thereof, a racemic mixture, and other steric isomers may be used in the same purpose.

Some of the compounds used in the present invention may be prepared by the method disclosed in EP-A 0281239 (corresponding to JP-A 64-052753), EP-A 0284180 (corresponding to JP-A 01-104040), EP-A 0289349 (corresponding to JP-A 01-151519), EP-A 0453127 (corresponding to JP-A 05-58992), EP-A 0690049 (corresponding to JP-A 08-48665) or US patent No. 5369127. The references as above are herein incorporated by reference. Alternatively, these compounds may be prepared by a process analogous to that described herein or by any process known in the art.

As mentioned above, one of the characteristics of the PG like compounds of the present invention is a PG-receptor (ex. EP, FP, IP, TP and DP-receptor) agonist activity. Accordingly, the PG like compounds used in the present invention include any of compounds having a PG-receptor agonist activity, irrespective to their structure.

The above described fatty acid derivatives of the present invention are effective in treating external secretion disorders, especially in treating hypolacrimation including disorders in basal tear secretion, as well as in improving and treating of dry-eye conditions (i.e. decreased lacrimal fluid secretion and accompanying corneal disorders). Further, said compounds are also effective in improving hyposalivation, as well as in improving and

treating of dry-mouth conditions. Therefore, the composition is useful for treatment of external secretion disorders, especially hypolacrimation including disorders in basal tear secretion and/or dry eye condition, or 5 hyposalivation and/or dry-mouth conditions.

The term "treatment" or "treating" used herein refers to any means of control of a condition of a subject including prevention, cure, relief of the condition, and arrestation or relief of development of the condition.

10 The subjects who are intended to be treated by the method of the present invention are those suffered from external secretion disorder including xerosises such as dry-eye syndrome (xerophthalmia), dry-mouth syndrome (xerostomia), dry-nose syndrome (xeromycteria), dry-skin 15 syndrome (xeroderma), dry-vagina syndrome (symptom of vaginal dryness); chronic pancreatitis, chronic gastritis, and chronic bronchitis due to the depression of external secretion. Especially, those with conditions which are likely to induce dry-eye syndrome include hypolacrimation, 20 alacrima, xerophtalmia, Sjögren's syndrome, dry keratoconjunctivitis, Stevens-Johnson syndrome, ocular pemphigoid, marginal blepharitis, diabetes, post cataract operation and allergic conjunctivitis. In addition, those 25 with dry-eye syndrome, which may be induced by aging, long term VDT operation, dryness of an air-conditioned

room.

Systemic factors which may cause dry-mouth syndrome includes febrile disease, hypohydremia, endocrinopathy (myxedema, Basedow's disease, diabetes insipidus, etc.), metabolic disorders (diabetes, uremia, liver cirrhosis, etc.), deficiency of vitamin A or B, autoimmune diseases (Sjögren's syndrome, progressive scleroderma, etc.), anemia, bleeding, aging, various medications (sedatives, parasympatholytic drugs, antihistamines, etc.).  
In addition, topical factors may include sialadenitis, atrophy of salivary gland, sequela of radiotherapy, malformation (edodermal dysplasia, etc) and so forth.

The external secretion disorders means a state where abnormal external secretion (i.e. decrease or stop of the secretion), which may be caused by any etiology, is observed, especially the state with abnormal lacrimal fluid secretion including basal tear secretion, and abnormal salivation.

The method of the present invention may be effectuated by administering a composition comprising a fatty acid derivative as an active ingredient to the subject either orally or parenterally. The dosage form of the composition may be eye drops, ophthalmic ointment, sublingual tablets, troches, chewable tablets, collutoriums, sprays, ointments, powders, granules, tablets, capsules,

suppository and vaginal suppository. Dosage forms for topical application, such as eyedrops, ophthalmic ointment, sublingual tablets and ointment are preferable. These dosage forms may be prepared according to any of  
5 conventional methods.

The composition of the present invention may be admixed with an appropriate pharmaceutically acceptable additive. The additive is a compound which may be used together with the unsaturated fatty acid derivative of the  
10 invention and may include excipient, diluent, filler, solvent, lubricant, adjuvant, binder disintegrator, coating agent, cupsulating agent, ointment base, suppository base, aerosol base, emulsifier, dispersant, suspending agent, thickener, isotonic agent, buffering agent, analgesia,  
15 preservative, anti oxidant, corrigent, flavor, colorant, and functional agent (for example, cyclodextrin and biodegradable polymer). The additive may be selected based on any of reference books on pharmaceuticals.

The composition of the present invention may further be admixed with any of pharmaceutically active agents in so far as said agent is compatible with the purpose of the present invention.

In the present invention, the "effective amount" of a fatty acid derivative may vary depending on the kind of  
25 the fatty acid used, the condition to be treated, age and

body weight of the patient, dosage form, duration of the treatment, desired therapeutic effect and so on. For example, when the composition to be used in the treatment is formulated as eyedrops, a dosage form containing 5 0.000001-10.0 wt%, preferably 0.00001-1.0 wt% of the fatty acid derivative may be administered several drops per one eye, preferably 1-4 drops, several times per day, preferably, 1-6 times per day. When it is formulated as a sublingual tablet, a dosage form containing 0.000001-10.0 wt%, 10 preferably 0.00001-1.0 wt% of the fatty acid derivative may be administered in the oral cavity several times, preferably 1-6 times per day. Further, when it is formulated as an ointment, topical administration of a dosage form containing 0.000001-10.0 wt%, preferably 0.00001-1.0 wt% of the fatty 15 acid derivative for several times, preferably, 1-6 times per day may provide an enough effect.

## EXAMPLES

The present invention will be illustrated in more detail by way of the following examples. These examples 20 should not be used as any limitation of the present invention.

Test Example 1: Effect on whole tear secretion of normal rabbits.

### (1) Test animals

25 Male Japanese albino rabbits (Std:JW/CSK) were

used.

(2)Method of administration

Ophthalmic solution comprising 0.001% of 13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>, as an active ingredient of the present invention was prepared and used as a test composition. As a control, the vehicle of said solution without the active ingredient was used.

Each of the compositions was instilled singly to eight eyes at the amount of 30 μ l/eye. After the administration, the time course of the tear secretion change was examined according to the following method.

(3)Examination

Whole tear secretion

Before (0 hour) and 0.5, 2, 4, and 6 hours after the instillation, the whole tear secretion was determined.

Under no anesthetization, one edge of the Schirmer's test strip (Showa Yakuhin Kako Co., Ltd., Lot No. 70080) was inserted into the conjunctival sac of the each test animal. One minute after, the strip was removed and the length of the moistened part was read from the scale provided on the strip to determine the amount of whole tear secretion.

(4)Result

The result of the whole tear secretion test is shown in the Table 1. No stimulating response, such as

rubor in the front of the eye was observed after the administration in both of the test animals and the control animals.

These data are shown simultaneously with the  
5 statistical analysis.

Table 1

	number of the eyes tested	time (hr)	whole tear secretion (mm/min.)
Control group	8	before the administration	5.5±0.3
	8	0.5	8.1±0.7
	8	2	8.3±0.8
	8	4	7.3±0.7
	8	6	7.1±0.7
test group 0.001%	8	before the administration	5.3±0.2
	8	0.5	17.0±0.5##
	8	2	14.1±0.5##
	8	4	11.7±0.6##
	8	6	10.5±1.0#

#p<0.05 ##p<0.01: comparison with the value at the corresponding time of the control group (Student's-t test).

According to the above result, the test group  
10 comprising the compound of the present invention as an active ingredient caused a significant increase of the amount of whole tear secretion at a dose which does not induce any stimulating response such as rubor in the front of the eye. Therefore, the compound of the present invention was revealed to have an activity to increase the amount of tear secretion without any stimulating response.  
15

Test Example 2: Effect of the compound on decreased whole tear secretion, decreased basal tear secretion and keratoepithelial lesion in rabbit dry-eye syndrome model, which was induced by trigeminal denervation.

5      (1) Test animals

Fifteen male Japanese albino rabbits (Std:JW/CSK) were used.

(2) Generating rabbit dry-eye syndrome model by trigeminal denervation.

10     i) Operational procedure

Urethane (ALDRICH) was administered i.p. at the dose of 1g/kg to the rabbits of which occipital hair had been shaved.

After disinfection of the shaved area, midline incision of the skin was made from the frontal bone to the ear root, and the muscular tissue around the periosteum, temporal bone and mandibular articular process were detached. After the detachment, a hole of 2 × 1.5 cm in size was made in the bone from the parietal medial region to the temporal region by means of the bone drill (URAWA KOGYO Co., Ltd. MINITOR C-130) under the surgical microscope (KONAN CAMERA R&I Inc., PMO-50). Then, the dura was detached from the cranial bone while cotton bud was kept inserted between the temporal bone and the dura. After the detachment was made up to the cranial

base, detachment was further made toward the medial border of the petrous part of temporal bone in the carnial cavity, to find the trigeminal nerve in the pretrous part. Then, the dura of about 1 to 2 mm on the nasal side of the 5 semilunar ganglion was incised. After the incision, the two branches of nerve fascicle, i.e. the first branch (ocular nerve) of the trigeminal nerve and the second branch (maxillary nerve) were pulled laterally and cut with corneoscleral scissors. Immediately after the operation, 10 miosis of the ipsilateral eye was confirmed and then the cotton kept inserted was removed, and the skin at the head was closed with suture. After the operation, an antibiotic (MYCILLIN SOL® Meiji) was administered i.m. at the dose of 0.1 ml/kg.

15 The trigeminal denervation was made only on the left eye side, while on the right eye side, no trigeminal denervation nor sham operation was made.

20 After the operation, animals in stable state and showed decreased whole tear secretion, decreased basal tear secretion, and keratoepithelial lesion were subjected to the following test.

(3) Method of administration.

25 13,14-dihydro-15-keto-16,16-difluoro-PGE, was used as an active ingredient of the present invention to prepare test eyedrops containing 0.0001% and 0.001% of

the compound. As a control, the vehicle of the eyedrops without the active ingredient was used.

Each of the compositions was instilled to the eyes everyday at the volume of 30  $\mu$  l/eye two times a day 5 (at 10:00 and 18:00) for two weeks. Five eyes per each of the test groups and the control group were treated and then examined for the whole tear secretion, the basal tear secretion and the keratoepithelial lesion as follows.

(4) Examination

10 i) Whole tear secretion (Schirmer's Test)

Before the start of the instillation (week 0), and 1, 2, and 3 weeks after the start, the whole tear secretion was measured two hours after the first instillation on the day of examination.

15 Under no anesthetization, one edge of the Schirmer's test strip (Showa Yakuhin Kako Co., Ltd., Lot No. 70080) was inserted into the conjunctival sac of each test animal. One minute after, the strip was removed and the length of the moistened part was read from the scale 20 provided on the strip to determine the amount of whole tear secretion.

ii) Basal tear secretion

Before the start of the instillation (week 0), and 1, 2, and 3 weeks after the start, the basal tear secretion was 25 measured 2 hours after the 1st instillation on the day of the

examination.

Keratoconjunctiva was anesthetized by instillation of 4% lidocaine (Xylocaine® 4% for ophthalmic solution; Fujisawa Pharmaceutical Co., Ltd.), the eye drops 5 and the tear around the eyelid were wiped off about 5 minutes after and loss of keratoconjunctival esthesia was confirmed with the Cochet-Bonnet type esthesiometer. Then, one edge of the Shirmer's test strip was inserted into the conjunctival sac and kept there for 5 minutes. The 10 length of the moistened part was read from the scale on the strip.

The basal tear secretion was expressed by mean value per minute calculated from the 4-minutes value obtained by subtracting the initial 1-minute value from the 15 5-minutes Sirmer's test, so that the spontaneous volume of the tear retained in the conjunctival sac might be excluded.

### iii) Keratoepithelial lesion

Before the start of instillation (week 0) and 1,2, and 3 weeks after the start, the keratoepithelial lesion was 20 evaluated two hours after the first instillation on the day of examination.

Each animal was placed in a stainless steel fixator, and given instillation of 50  $\mu$ l of the mixture of 1% rose bengal and 1% fluorescein to stain their 25 keratoconjunctival epithelium. Stained area, i.e. the

abnormal area on the epithelium was evaluated according to the criteria shown in the Table 2.

Table 2

Scores	Stained area of the keratoconjunctiva
0	None
0.5	only a part was stained slightly
1	the area was less than 1/4
2	the area was more than 1/4 and less than 1/2
3	the area was more than 1/2 and less than 3/4
4	the area was more than 3/4

(5) Results

5 The result of the whole tear secretion is shown in the Table 3, that of the basal tear secretion is shown in the Table 4, and that of the keratoepithelial lesion is shown in the Table 5. Statistical analysis is also shown with the data.

Table 3

	number of eyes	time (weeks)	whole tear secretion (mm/min.)
before the operation	15	-	5.23 ± 0.33
after the operation	15	-	3.10 ± 0.28 **
control group	5	before administration	3.10 ± 0.40 **
	5	1	4.40 ± 1.21
	5	2	3.80 ± 0.64 *
	5	3	3.90 ± 0.90
test group 0.0001%	5	before administration	3.00 ± 0.61 **
	5	1	7.10 ± 0.51 ***++
	5	2	6.60 ± 0.37 *##++
	5	3	6.30 ± 0.68 ++
test group 0.001%	5	before administration	3.20 ± 0.51 **
	5	1	11.20 0.51 ***##++ ±
	5	2	10.50 0.57 ***##++ ±
	5	3	9.90 0.81 ***##++ ±

\*p<0.05    \*\*p<0.01 :comparison with the value before the operation(Student's-t test)

+p<0.05    ++p<0.01 :comparison with the value at the corresponding time in the control group(Student's t-test)

#p<0.05    ##p<0.01 :comparison with the value of time 0 (before administration) in each treatment group.

Table 4

	number of eyes	time (weeks)	basal tear secretion (mm/min.)
before the operation	15	-	1.45±0.10
after the operation	15	-	0.43±0.05 <sup>[**]</sup>
control group	5	before administration	0.43±0.10 <sup>**</sup>
	5	1	0.88±0.21 <sup>*</sup>
	5	2	0.73±0.22 <sup>**</sup>
	5	3	0.73±0.18 <sup>**</sup>
test group 0.0001%	5	before administration	0.43±0.06 <sup>[**]</sup>
	5	1	1.53±0.26 <sup>[+]</sup>
	5	2	1.60±0.11 <sup>***</sup>
	5	3	1.48±0.17 <sup># [++]</sup>
test group 0.001%	5	before administration	0.43±0.08 <sup>**</sup>
	5	1	2.00 <sup>±</sup> 0.12 <sup>*###++</sup>
	5	2	2.00 <sup>±</sup> 0.18 <sup>*###++</sup>
	5	3	2.00 <sup>±</sup> 0.14 <sup>*###++</sup>

[\*\*]p<0.01 :comparison with the value before the

operation (Aspin-Welch test)

\*p<0.05 \*\*p<0.01 :comparison with the value before the  
5 operation in each group (student's-t test)

++p<0.01 :comparison with the value at the  
corresponding time in the control group (Student's t-test)

[+]p<0.05 [++]p<0.01 :comparison with the value at the  
corresponding time in the control group (Aspin-Welch test)

# $p<0.05$  ## $p<0.01$  :comparison with the value of time 0  
(before administration) in each test group (Student's-t test).

Table 5

	number of eyes	time (weeks)	Keratoepithelial lesion (score)
before the operation	15	-	$0.07 \pm 0.05$
after the operation	15	-	$2.93 \pm 0.15^{[**]}$
control group	5	before administration	$2.80 \pm 0.20^{[**]}$
	5	1	$1.90 \pm 0.51^{[**]}$
	5	2	$1.60 \pm 0.58^{[**]}$
	5	3	$1.50 \pm 0.32^{[**]++}$
	5	before administration	$3.00 \pm 0.32^{[**]}$
test group 0.0001%	5	1	$1.00 \pm 0.27^{[*]++}$
	5	2	$0.50 \pm 0.16^{[*]++}$
	5	3	$0.40 \pm 0.19^{*++}$
	5	before administration	$3.00 \pm 0.32^{[**]}$
	5	1	$0.70 \pm 0.34^{++}$
test group 0.001%	5	2	$0.10 \pm 0.10^{[++]}$
	5	3	$0.10 \pm 0.10^{[##][++]}$

[\*] $p<0.05$  [\*\*] $p<0.01$  :comparison with the value before the  
5 operation (Aspin-Welch test)

++ $p<0.01$  :comparison with the value before the  
operation in each group (student's-t test)

[++] $p<0.01$  :comparison with the value at the  
corresponding time in the control group (Aspin-Welch test)

10 [#] $p<0.01$  :comparison with the value of time 0  
(before administration) in each test group (Aspin-Welch

test).

Based on the above results, the test group comprising the compound of the present invention as an active ingredient improved the decreased whole tear secretion and basal tear secretion as well as keratoconjunctival lesion accompanied by the decrease of the tear secretion observed in the dry-eye syndrome model animals. Therefore, the composition of the present invention is appear to be useful for treatment of hypolacrimation including disorders in basal tear secretion as well as dry-eye conditions i.e. hypolacrimation and accompanying keratoconjunctival lesion.

#### Test example 3: Exaltation of salivation

The effect of the composition of the present invention on salivary secretion was determined.

##### (1) Test animals

Male and female rats (Crj:CD strain) were used. Each of the test and control groups contains 16 animals.

##### (2) Method of administration

13,14-dihydro-15-keto-16,16-difluoro-PGE, was used as an active ingredient of the present invention to prepare test solution containing 0.2mg/ml of the compound. .

5 ml/kg of the solution (1 mg/kg of the compound) was forcedly administrated orally once a day. For the

animals of control group, 5 ml/kg of the vehicle without the active ingredient was administrated once a day. The administration was continued for four weeks.

(3) Examination

5 The amount of the saliva of the test group and control group was evaluated visually everyday.

(4) Result

In the group of the animals administered with the fatty acid derivative of the present invention, exaltation of 10 saliva was observed in 8 of 16 rats on the 10th day after the start of the administration, and after that, the number of the rats with salivary exaltation was increased time dependently. Subsequent to the 22nd day after the start, each of 16 rats administrated with the composition showed 15 salivary exaltation. Whereas, in the control group, all animals kept the normal salivary secretion over the whole administration term.

**Test Example 4: Exaltation of salivation**

The effect of the composition of the present 20 invention on salivary secretion was determined.

(1) Test animals

Male rats(SD strain) were used.

Each of the test and control groups contains 8 animals.

(2) Method of administration

25 13,14-dihydro-15-keto-16,16-difuloro-PGE, was

used as an active ingredient of the present invention to prepare test solution containing 0.2mg/ml of the compound.

5 ml/kg of the solution (1.0 mg/kg of the compound) was forcedly administrated orally once a day.

5 For the animals f control group, 5 ml/kg of 1% polysorbate was administrated once a day. The administration was continued for 10 days.

### (3) Examination

The amount of the saliva of the test group and 10 control group was measured one hour after the administration on 10th day. The edge of a paper filter (Schirmer's test strip, Showa Yakuhin Kako Co., Ltd.) was inserted between lower gingiva and mandibula. Three minutes after, the paper filter was removed and the weight 15 of the saliva was calculated by the following formula.

weight of saliva = (the weight of paper filter including saliva) - ( weight of only paper filter)

### (4) Result

The result of the salivary secretion is shown in the 20 table 6.

Table 6

	Number of animals	Salivary weight (mg, mean $\pm$ S.E.)
Control group	8	4.6 $\pm$ 0.9
Test group	8	18.1 $\pm$ 5.6*

\*P<0.05, compared with control group(U-test of Mann-Whitney)

5 In the group of the animals administered with the fatty acid derivative of the present invention, salivary secretion was significantly increased compared with that of the control group.

10 Test Example 5:Effect on whole tear secretion of normal rabbits.

(1) Test animals

Male Japanese albino rabbits were used.

(2) Method of administration

15 Ophthalmic solution comprising an active ingredient of the present invention was prepared and used as a test composition.

Each of the compositions was instilled to the eye singly at the amount of 30  $\mu$  l/eye.

(3) Examination

20 Amount of the tear secretion

Before (0 hour) and 2 hours after the instillation, the whole tear secretion was determined.

Under no anesthetization, one edge of the Schirmer's test strip (Showa Yakuhin Kako Co., Ltd.) was inserted into the conjunctival sac of the each test animal. One minute after, the strip was removed and the length of the moistened part was read from the scale provided on the strip to determine the amount of whole tear secretion.

The rate (%) of increased amount of whole tear secretion was calculated at the 2 hours after the instillation compared with the before (0 hour).

#### 10 (4) Result

The result of the whole tear secretion test is shown in the Table 7. In addition to the data in the table, no stimulating response, such as rubor, in the front of the eye was observed after the administration of test compounds.

Table 7

Test compound	Concentration of the test compound	Number of the eyes tested	Ratio of increased whole tear secretion (%)
Compound 1	30 $\mu$ g/g	4	40.7
Compound 2	10 $\mu$ g/g	4	52.5
Compound 3	10 $\mu$ g/g	4	52.0
Compound 4	3 $\mu$ g/g	4	61.8
Compound 5	3 $\mu$ g/g	4	43.5
Compound 6	100 $\mu$ g/g	4	44.0
Compound 7	2000 $\mu$ g/g	4	56.9
Compound 8	1 $\mu$ g/g	4	24.8

Compound 1: 15-dehydroxy-13,14-dihydro-14,15-dehydro-16-keto-17,17-difluoro-PGE,-methyl ester

Compound 2: 13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGE<sub>1</sub>,

Compound 3: 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>,

5 Compound 4: 13,14-dihydro-15-keto-16,16-difluoro-PG<sub>2a</sub>-methyl ester

Compound 5: 11-dehydroxy-13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>,

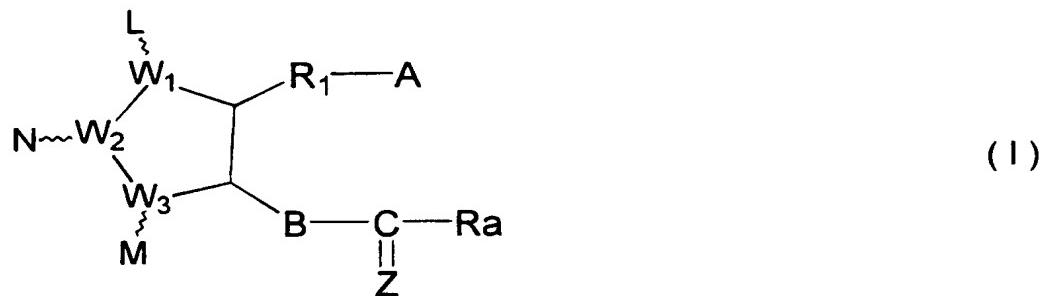
Compound 6: 13,14-dihydro-15-keto-PGE<sub>1</sub>,

10 Compound 7: 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGE<sub>1</sub>-isopropyl ester

Compound 8: 13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>2</sub>

## Claims

1. A composition for treatment of external secretion disorders, which comprises, a fatty acid derivative as an active ingredient.
- 5 2. The composition of claim 1, which is used for treatment of dry-eye syndrome.
3. The composition of claim 1, which is used for treatment of hypolacrimation.
- 10 4. The composition of claim 1, which is used for treatment of dry-mouth syndrome.
5. The composition of claim 1, which is used for treatment of hyposalivation.
6. The composition of claim 1, wherein the fatty acid derivative is an unsaturated fatty acid.
- 15 7. The composition of claim 1, wherein the fatty acid derivative is a prostaglandin like compound.
8. The composition of claim 7, wherein the prostaglandin like compound is a PG receptor agonist.
9. The composition of claim 1, wherein the fatty acid derivative is the one represented by the general formula (I):
- 20



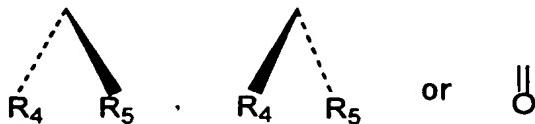
wherein  $W_1$ ,  $W_2$  and  $W_3$  are carbon or oxygen atom,

L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or its functional derivative;

B is single bond,  $-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$ ,  $-\text{C}\equiv\text{C}-$ ,  $-\text{CH}_2-\text{CH}_2\text{-CH}_2-$ ,  $-\text{CH}=\text{CH-CH}_2-$ ,  $-\text{CH}_2-\text{CH=CH-}$ ,  $-\text{C}\equiv\text{C-CH}_2-$ , or  $-\text{CH}_2-\text{C}\equiv\text{C-}$ ;

Z is



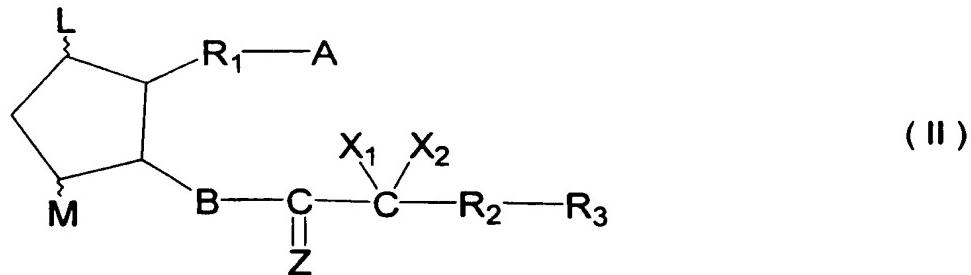
wherein  $R_4$  and  $R_5$  are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein  $R_4$  and  $R_5$  are not hydroxy and lower alkoxy at the same time;

$R_1$  is a divalent saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkyl, aryl or heterocyclic; and

$R_a$  is a saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, lower alkyl, hydroxy, lower

alkoxy, lower alkanoyloxy, cyclo(lower)alkyl,  
 cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic or  
 heterocyclic-oxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy;  
 aryl; aryloxy; heterocyclic; heterocyclic-oxy.

5 10. The composition of claim 1, wherein the fatty acid derivative is the one represented by the general formula (II):

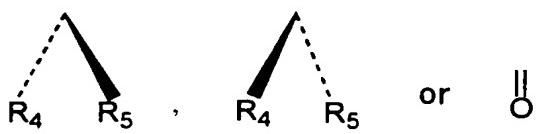


wherein L and M are hydrogen, hydroxy, halogen,  
 10 lower alkyl, hydroxy(lower)alkyl or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is -CH<sub>2</sub>OH, -COCH<sub>2</sub>OH, -COOH or its functional derivative;

15 B is single bond, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -C≡C-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH=CH-, -C≡C-CH<sub>2</sub>-, or -CH<sub>2</sub>-C≡C-;

Z is

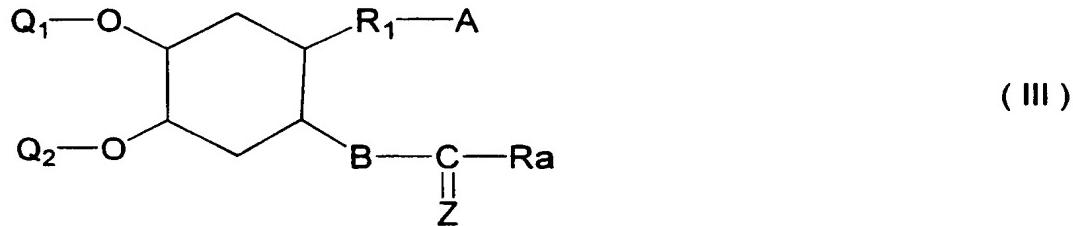


wherein R<sub>4</sub> and R<sub>5</sub> are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R<sub>4</sub> and R<sub>5</sub> are not hydroxy and lower alkoxy at the same time;

5        X<sub>1</sub> and X<sub>2</sub> are hydrogen, lower alkyl or halogen;  
 R<sub>1</sub> is a divalent saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkyl, aryl or heterocyclic;

10      R<sub>2</sub> is a single bond or lower alkylene; and  
 R<sub>3</sub> is lower alkyl, lower alkoxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic or heterocyclic-oxy.

11.      The composition of claim 1, wherein the fatty acid derivative is the one represented by the formula (III):



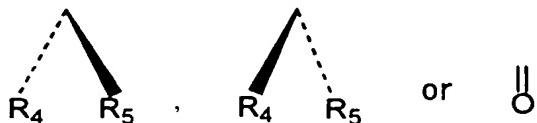
20      wherein Q<sub>1</sub> and Q<sub>2</sub> are hydrogen or lower alkyl, or Q<sub>1</sub> and Q<sub>2</sub> are linked together to form -(CH<sub>2</sub>)<sub>n</sub>- wherein n is 1, 2 or 0, and six-membered ring may have at least one double bond;

A is -CH<sub>2</sub>OH, -COCH<sub>2</sub>OH, -COOH or its functional

derivative;

B is single bond, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -C≡C-, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH=CH-, -C≡C-CH<sub>2</sub>-, or -CH<sub>2</sub>-C≡C-;

5 Z is



wherein R<sub>4</sub> and R<sub>5</sub> are hydrogen, hydroxy, halogen,  
 10 lower alkyl, lower alkoxy or hydroxy(lower)alkyl,  
 wherein R<sub>4</sub> and R<sub>5</sub> are not hydroxy and lower alkoxy at  
 the same time;

R<sub>1</sub> is a divalent saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or  
 15 substituted by halogen, oxo, hydroxy, lower alkyl, aryl or heterocyclic;

R<sub>a</sub> is a saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, lower alkyl, hydroxy, lower  
 20 alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic or heterocyclic-oxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic; heterocyclic-oxy; and

the six-memberd ring may optionally have one or more  
 25 double bonds and may optionally consist a conjugated

system.

12. The composition of claim 1, which is in a dosage form suitable for ophthalmic administration.

13. The composition of claim 12, which is formulated 5 as eye drops.

14. The composition of claim 1, which is in a dosage form suitable for administrating into the oral cavity.

15. The composition of claim 14, which is formulated as sublingual tablet.

10 16. A method for treatment of external secretion disorders, which comprises administering an effective amount of a fatty acid derivative to a subject in need of said treatment.

17. The method of claim 16, wherein said external 15 disorder is dry-eye syndrome.

18. The method of claim 16, wherein said external disorder is hypolacrimation.

19. The method of claim 16, wherein said external disorder is dry-mouth syndrome.

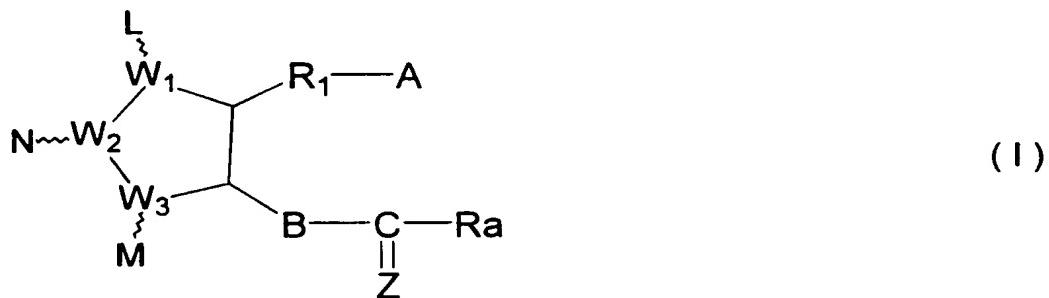
20 20. The method of claim 16, wherein said external disorder is hyposalivation.

21. The method of claim 16, wherein the fatty acid derivative is an unsaturated fatty acid.

22. The method of claim 16, wherein the fatty acid 25 derivative is a prostaglandin like compound.

23. The method of claim 22, wherein the prostaglandin like compound is a PG receptor agonist.

24. The method of claim 16, wherein the fatty acid derivative is the one represented by the general formula (I):



5

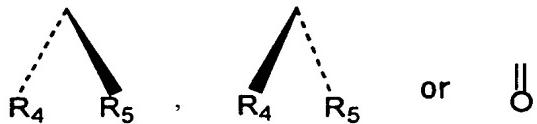
wherein  $W_1$ ,  $W_2$  and  $W_3$  are carbon or oxygen atom,

$L$ ,  $M$  and  $N$  are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, or oxo, wherein at least one of  $L$  and  $M$  is a group other than hydrogen, and the five-membered ring may have at least one double bond;

$A$  is  $-CH_2OH$ ,  $-COCH_2OH$ ,  $-COOH$  or its functional derivative;

$B$  is single bond,  $-CH_2-CH_2-$ ,  $-CH=CH-$ ,  $-C\equiv C-$ ,  $-CH_2-CH_2-CH_2-$ ,  $-CH=CH-CH_2-$ ,  $-CH_2-CH=CH-$ ,  $-C\equiv C-CH_2-$ , or  $-CH_2-C\equiv C-$ ;

$Z$  is



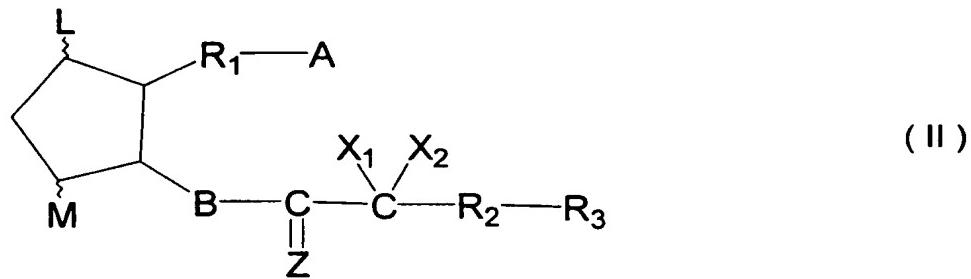
wherein  $R_4$  and  $R_5$  are hydrogen, hydroxy, halogen,

lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R<sub>4</sub> and R<sub>5</sub> are not hydroxy and lower alkoxy at the same time;

R<sub>1</sub> is a divalent saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkyl, aryl or heterocyclic ; and

R<sub>a</sub> is a saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic or heterocyclic-oxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic; heterocyclic-oxy.

25. The method of claim 16, wherein the fatty acid derivative is the one represented by the general formula (II):



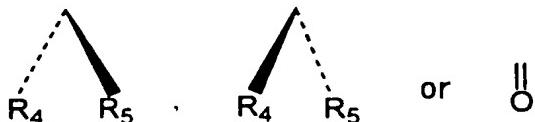
wherein L and M are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl or oxo, wherein at least one of L and M is a group other than hydrogen, and the

five-membered ring may have at least one double bond;

A is -CH<sub>2</sub>OH, -COCH<sub>2</sub>OH, -COOH or its functional derivative;

B is single bond, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -C≡C-, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH=CH-, -C≡C-CH<sub>2</sub>-, or -CH<sub>2</sub>-C≡C-;

Z is



wherein R<sub>4</sub> and R<sub>5</sub> are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R<sub>4</sub> and R<sub>5</sub> are not hydroxy and lower alkoxy at the same time;

X<sub>1</sub> and X<sub>2</sub> are hydrogen, lower alkyl or halogen;

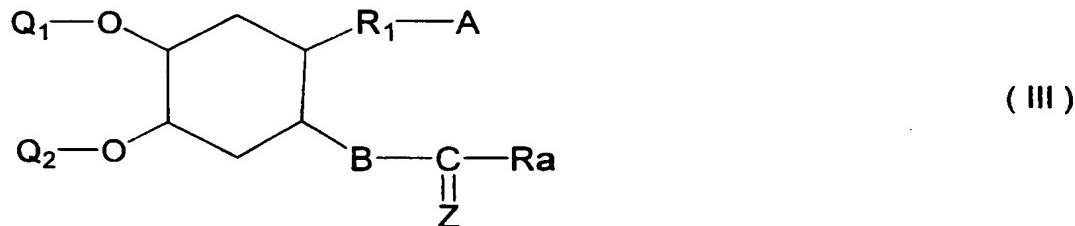
R<sub>1</sub> is a divalent saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkyl, aryl or heterocyclic;

R<sub>2</sub> is a single bond or lower alkylene; and

R<sub>3</sub> is lower alkyl, lower alkoxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic or heterocyclic-oxy.

25 26. The method of claim 16, wherein the fatty acid

derivative is the one represented by the formula (III):



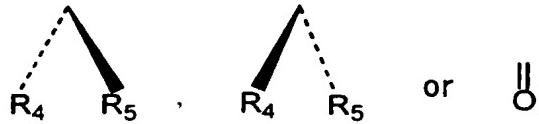
5 wherein  $Q_1$  and  $Q_2$  are hydrogen or lower alkyl, or  $Q_1$  and  $Q_2$  are linked together to form  $-(CH_2)_n-$  wherein  $n$  is 1, 2 or 0, and six-membered ring may have at least one double bond;

10 A is  $-CH_2OH$ ,  $-COCH_2OH$ ,  $-COOH$  or its functional derivative;

B is single bond,  $-CH_2-CH_2-$ ,  $-CH=CH-$ ,  $-C\equiv C-$ ,  $-CH_2-CH_2-$ ,  $-CH=CH-CH_2-$ ,  $-CH_2-CH=CH-$ ,  $-C\equiv C-CH_2-$ , or  $-CH_2-C\equiv C-$ ;

Z is

15



wherein  $R_4$  and  $R_5$  are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl,

20 wherein  $R_4$  and  $R_5$  are not hydroxy and lower alkoxy at the same time;

$R_1$  is a divalent saturated or unsaturated lower-medium

aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkyl, aryl or heterocyclic;

R<sub>a</sub> is a saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic or heterocyclic-oxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic; heterocyclic-oxy; and

the six-membered ring may optionally have one or more double bonds and may optionally consist a conjugated system.

27. The method of claim 16, which comprises administering ophthalmically a composition comprising a fatty acid derivative formulated in a dosage form suitable for ophthalmic administration.

28. The method of claim 27, wherein said composition is formulated as eye drops.

29. The method of claim 16, which comprises to orally administrate to the subject a composition comprising a fatty acid derivative formulated in a dosage form suitable for administrating into the oral cavity.

30. The method of claim 29, wherein said composition is formulated as a sublingual tablet.

31. Use of a fatty acid derivative for producing a pharmaceutical composition for the treatment of external secretion disorders.

32. The use of claim 31, wherein said external disorder is dry-eye syndrome.

33. The use of claim 31, wherein said external disorder is hypolacrimation.

34. The use of claim 31, wherein said external disorder is dry-mouth syndrome.

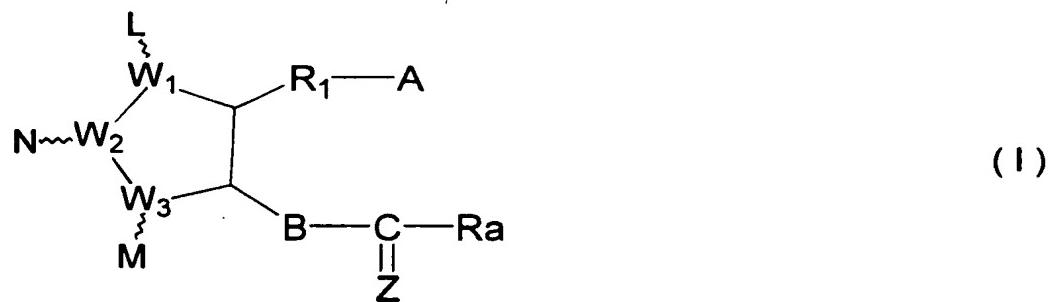
10 35. The use of claim 31, wherein said external disorder is hyposalivation.

36. The use of claim 31, wherein the fatty acid derivative is an unsaturated fatty acid.

15 37. The use of claim 31, wherein the fatty acid derivative is a prostaglandin like compound.

38. The use of claim 37, wherein the prostaglandin like compound is a PG receptor agonist.

39. The use of claim 31, wherein the fatty acid derivative is the one represented by the general formula (I):



20

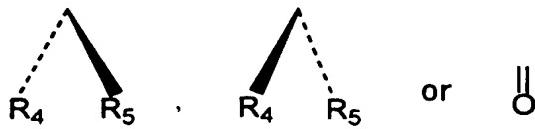
wherein  $W_1$ ,  $W_2$  and  $W_3$  are carbon or oxygen atom,

L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

5 A is -CH<sub>2</sub>OH, -COCH<sub>2</sub>OH, -COOH or its functional derivative;

B is single bond, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -C≡C-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH=CH-, -C≡C-CH<sub>2</sub>-, or -CH<sub>2</sub>-C≡C-;

10 Z is



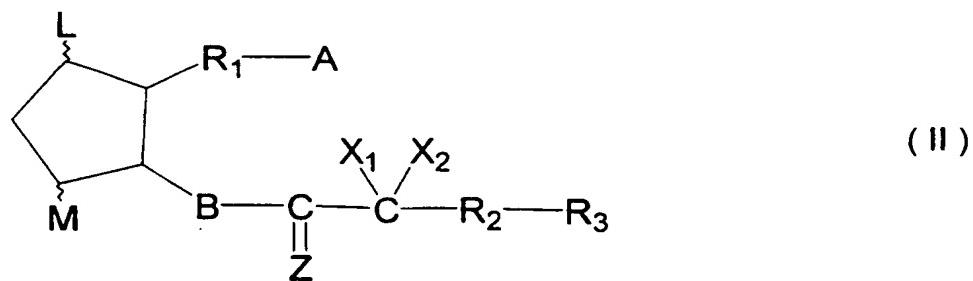
wherein R<sub>4</sub> and R<sub>5</sub> are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R<sub>4</sub> and R<sub>5</sub> are not hydroxy and lower alkoxy at the same time;

15 R<sub>1</sub> is a divalent saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkyl, aryl or heterocyclic; and

20 Ra is a saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl,

cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic or heterocyclic-oxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic; heterocyclic-oxy.

40. The use of claim 31, wherein the fatty acid derivative is the one represented by the general formula 5 (II):

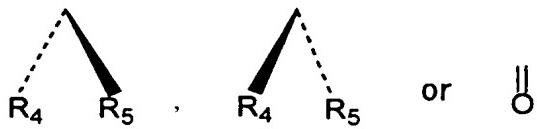


wherein L and M are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl or oxo, wherein at least 10 one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is -CH<sub>2</sub>OH, -COCH<sub>2</sub>OH, -COOH or its functional derivative;

B is single bond, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -C≡C-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH=CH-, -C≡C-CH<sub>2</sub>-, or -CH<sub>2</sub>-C≡C-;

Z is



wherein R<sub>4</sub> and R<sub>5</sub> are hydrogen, hydroxy, halogen,

lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R<sub>4</sub> and R<sub>5</sub> are not hydroxy and lower alkoxy at the same time;

X<sub>1</sub> and X<sub>2</sub> are hydrogen, lower alkyl or halogen;

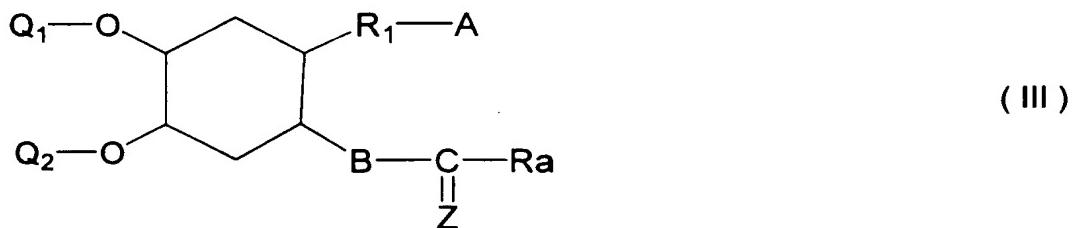
5 R<sub>1</sub> is a divalent saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkyl, aryl or heterocyclic;

R<sub>2</sub> is a single bond or lower alkylene; and

10 R<sub>3</sub> is lower alkyl, lower alkoxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic or heterocyclic-oxy.

41. The use of claim 31, wherein the fatty acid derivative is the one represented by the formula (III):

15



wherein Q<sub>1</sub> and Q<sub>2</sub> are hydrogen or lower alkyl, or Q<sub>1</sub> and Q<sub>2</sub> are linked together to form -(CH<sub>2</sub>)<sub>n</sub>- wherein n is 1,

2 or 0, and six-membered ring may have at least one double

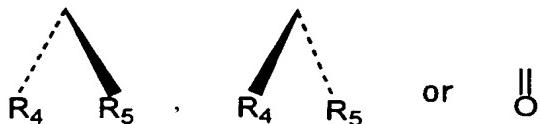
20 bond;

A is -CH<sub>2</sub>OH, -COCH<sub>2</sub>OH, -COOH or its functional derivative;

B is single bond, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -C≡C-, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH=CH-, -C≡C-CH<sub>2</sub>-, or -CH<sub>2</sub>-C≡C-;

Z is

5



wherein R<sub>4</sub> and R<sub>5</sub> are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl,

10 wherein R<sub>4</sub> and R<sub>5</sub> are not hydroxy and lower alkoxy at the same time;

R<sub>1</sub> is a divalent saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkyl, aryl or heterocyclic;

R<sub>a</sub> is a saturated or unsaturated lower-medium aliphatic hydrocarbon residue, which is unsubstituted or substituted by halogen, oxo, lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic or heterocyclic-oxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic; heterocyclic-oxy; and

25 the six-membered ring may optionally have one or more double bonds and may optionally consist a conjugated system.

42. The use of claim 31, wherein said composition is suitable for ophthalmic administration.

43. The use of claim 42, wherein said composition is formulated as eye drops.

5 44. The use of claim 31, wherein said composition is suitable for administrating into the oral cavity.

45. The use of claim 44, wherein said composition is formulated as sublingual tablet.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number  
**WO 01/05388 A3**

(51) International Patent Classification<sup>7</sup>: A61K 31/201. (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(21) International Application Number: PCT/JP00/04696

(22) International Filing Date: 13 July 2000 (13.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/143,627 14 July 1999 (14.07.1999) US

(71) Applicant: SUCAMPO, A.G. [CH/CH]: Graben 5,  
CH-6300 Zug (CH).

(72) Inventor: UENO, Ryuji: 11025 Stanmore Drive, Potomac, Montgomery, MD 20854 (US).

(74) Agents: AOYAMA, Tamotsu et al.: Aoyama & Partners, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540-0001 (JP).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(88) Date of publication of the international search report:  
— with international search report

10 May 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/05388 A3

(54) Title: USE OF A FATTY DERIVATIVE FOR THE TREATMENT OF EXTERNAL SECRETIONDISORDERS

(57) Abstract: Disclosed is a composition for treatment of external secretion disorders comprising, as an active ingredient a fatty acid derivative. The composition of the present invention is useful for treatment of at least one condition selected from hypolacrimation including disorder of basal tear secretion, dry-eye syndrome, hyposalivation and dry-mouth syndrome.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/04696

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/201 A61K31/202 A61K31/5575 A61P27/02 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE, MEDLINE, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 00 38690 A (ALCON LAB INC ;KLIMKO PETER G (US)) 6 July 2000 (2000-07-06)  the whole document ---	1-3, 7-10,12, 13, 16-18, 22-25, 27,28, 31-33, 37-40, 42,43

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

24 July 2001

Date of mailing of the international search report

06.08.01

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
Fax: (+31-70) 340-3016

Authorized officer

Hoff, P

## INT'L NATIONAL SEARCH REPORT

International Application No
PCT/JP 00/04696

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 38663 A (SHARIF NAJAM A ;ALCON LAB INC (US)) 6 July 2000 (2000-07-06)  the whole document ---	1-3, 7-10,12, 13, 16-18, 22-25, 27,28, 31-33, 37-40, 42,43
P,X	S. GIUFFRIDA ET AL.: "Essential Fatty Acids (Linoleic and Gamma-Linolenic Acids) on Tear Deficient Dry-Eye Treatment" INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, vol. 41, no. 4, 15 March 2000 (2000-03-15), page s275 XP000991088 the whole document ---	1-3,6, 14, 16-18, 21,29, 31-33, 36,44
X	WO 97 16179 A (ALCON LAB INC) 9 May 1997 (1997-05-09)  the whole document ---	1-3,6, 12,13, 16-18, 21,27, 28, 31-33, 36,42,43
X	EP 0 019 423 A (EFAMOL LTD) 26 November 1980 (1980-11-26)  page 21, line 12 -page 22, line 30; claims page 1, line 1 - line 12 ---	1-10, 12-14, 16-25, 27-29, 31-40, 42-44
X	HORROBIN D.F. ET AL: "Sjogren's syndrome and the sicca syndrome: The role of prostaglandin E1 deficiency. Treatment with essential fatty acids and vitamin C" MEDICAL HYPOTHESES_( <u>MED. HYPOTHESES_</u> ), 6/3 (225-232), XP000991548 United Kingdom the whole document ---	1-10, 12-14, 16-25, 27-29, 31-40, 42-44

-/--

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/04696

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MANTHORPE R ET AL: "Primary Sjogren's syndrome treated with Efamol/Efavit. A double-blind cross-over investigation." RHEUMATOLOGY INTERNATIONAL, 1984, 4 (4) P165-7, XP000991010 GERMANY, WEST the whole document ---	1-6, 14, 16-21, 29, 31-36, 44
X	EP 0 132 089 A (EFAMOL LTD) 23 January 1985 (1985-01-23)	1-3, 6, 14, 16-18, 21, 29, 31-33, 36, 44
X	abstract page 5, line 1 - line 15; claims ---	
X	PHELPS BROWN N.A. ET AL: "Nutrition supplements and the eye" EYE_(EYE_), 1998, 12/1 (127-133), XP000991021 United Kingdom	1-3, 6, 14, 16-18, 21, 29, 31-33, 36, 44
X	abstract page 130, right-hand column, last paragraph -page 131, left-hand column, paragraph 1 ---	
X	D.F. HORROBIN ET AL.: "ESSENTIAL FATTY ACID METABOLISM IN DISEASES OF CONNECTIVE TISSUE WITH SPECIAL REFERENCE TO SCLERODERMA AND TO SJOGREN'S SYNDROME" MEDICAL HYPOTHESES, vol. 14, no. 3, 1984, pages 233-248, XP000991412 abstract page 240, last paragraph ---	1-3, 6, 14, 16-18, 21, 29, 31-33, 36, 44
X	WO 90 01323 A (BERNSTEIN JOEL E) 22 February 1990 (1990-02-22) the whole document ---	1, 6, 16, 21, 31, 36
X	PATENT ABSTRACTS OF JAPAN vol. 013, no. 101 (C-574), 9 March 1989 (1989-03-09) & JP 63 277604 A (SHOWA DENKO KK), 15 November 1988 (1988-11-15) abstract ---	1, 6, 16, 21, 31, 36
		-/-

## INTE NATIONAL SEARCH REPORT

International Application No

PCT/JP 00/04696

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	N. TAIRA ET AL.: "Mode of actions of prostaglandins E2, F1alpha and F2alpha in the dog salivary gland" INT UNION PHARMACOL PROCEEDINGS OF THE INTERNATIONAL CONGRESS OF PHARMACOLOGY, 1977, page 159 XP001011501  the whole document ---	1,4,5, 7-10,14, 16,19, 20, 22-25, 29,31, 34,35, 37-40,44
X	N. TAIRA ET AL.: "Prostaglandin F2alpha as a potent excitant of the parasympathetic postganglionic neurons of the dog salivary gland" LIFE SCIENCES, vol. 13, no. 5, 1973, pages 501-506, XP001011455  the whole document ---	1,4,5, 7-10,14, 16,19, 20, 22-25, 29,31, 34,35, 37-40,44
X	N. TAIRA ET AL.: "Differential effects of tetrodotoxin on the sialogenous and vasodilator actions of prostaglandin E2 in the dog salivary gland" LIFE SCIENCES, vol. 15, no. 5, 1974, pages 987-993, XP001011500  the whole document ---	1,4,5, 7-10,14, 16,19, 20, 22-25, 29,31, 34,35, 37-40,44
X	C. PHOLPRAMOO ET AL.: "Secretory effect of prostaglandins on the rabbit lacrimal gland in vivo" PROSTAGLANDINS AND MEDICINE, vol. 3, no. 3, 1979, pages 185-192, XP001011481  the whole document ---	1-3, 7-10,12, 13, 16-18, 22-25, 27,28, 31-33, 37-40, 42,43
X	EP 0 503 887 A (UENO SEIYAKU OYO KENKYUJO KK) 16 September 1992 (1992-09-16)  abstract page 3, line 1 - line 12 page 32, line 1 - line 54; claims; examples --- -/-	1-5, 7-10, 12-15

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/04696

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 308 135 A (UENO SEIYAKU OYO KENKYUJO KK) 22 March 1989 (1989-03-22)	1-5, 7-10, 12-15
A	see whole document, in particular Table 1, page 23, line 20 and page 25, line 50 -----	16-18, 22-25, 27,28, 31-33, 37-40, 42,43
X	WO 94 24121 A (ALLERGAN INC) 27 October 1994 (1994-10-27)	1-5, 11-14
A	the whole document -----	26,41
A	F.M.C. DE FARIAS : "Prostaglandin analogues: the synthesis of new prostanoids from natural safrole" QUIMICA NOVA, vol. 7, no. 2, 1984, pages 111-112, XP001011499 the whole document -----	11,26,41

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/JP 00/04696

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  

Although claims 16–30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  

see FURTHER INFORMATION sheet PCT/ISA/210
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-45 relate to an extremely large number of possible compounds (fatty acid derivatives/unsaturated fatty acids; prostaglandin like compound/compounds of the general formulae (I) and (II); compounds of the general formula (III)). Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Furthermore, present claims 1,16,31 relate to an extremely large number of possible diseases to treat (any external secretion disorders). Again, support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found for only a very small proportion of the diseases claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to:

- the compounds specifically identified in the description on page 10, lines 2-6
- the prostaglandins tested in the examples and based on those compounds, a generalisation of their structural formulae to encompass compounds having the following structural features: compounds of formula (II) with L and M = hydroxy or oxo; A = COOH (or salt, ester and amide thereof); B= CH<sub>2</sub>-CH<sub>2</sub> and Z= oxo; X<sub>1</sub> and X<sub>2</sub> are such that at least one of them is halogen; R<sub>1</sub> being a hydrocarbon containing 2-10 carbon atoms
- the compounds of formula (III) which is benzene ring type compound with A = COOH (or salt, ester and amide thereof); B is a single bond; Z is hydroxy and R<sub>1</sub> is as defined on page 25
- the diseases mentioned in claims 2-5,17-20, 32-35,

with due regard to the general idea underlying the present invention.

Claims searched incompletely: 1-45

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/JP 00/04696

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0038690 A	06-07-2000	AU 2183800 A		31-07-2000
WO 0038663 A	06-07-2000	AU 2183900 A		31-07-2000
WO 9716179 A	09-05-1997	US 5696166 A AT 198044 T AU 706373 B AU 6851696 A CA 2234367 A DE 69611251 D DE 69611251 T DK 858330 T EP 0858330 A ES 2152556 T JP 11515024 T PT 858330 T		09-12-1997 15-12-2000 17-06-1999 22-05-1997 09-05-1997 18-01-2001 05-04-2001 02-01-2001 19-08-1998 01-02-2001 21-12-1999 30-03-2001
EP 0019423 A	26-11-1980	AT 7856 T AU 534010 B AU 5850280 A CA 1136044 A CA 1149739 A CA 1149740 A DE 3068172 D IE 49783 B JP 2075146 C JP 6197735 A JP 7079662 B JP 1833101 C JP 3069888 B JP 55162716 A US 4388324 A US 4535093 A US RE31836 E		15-06-1984 22-12-1983 20-11-1980 23-11-1982 12-07-1983 12-07-1983 19-07-1984 11-12-1985 25-07-1996 19-07-1994 30-08-1995 29-03-1994 05-11-1991 18-12-1980 14-06-1983 13-08-1985 19-02-1985
EP 0132089 A	23-01-1985	AT 96313 T AU 562938 B AU 3057784 A CA 1251736 A DE 3486235 D DE 3486235 T HK 37694 A IE 61082 B JP 60038324 A SG 25594 G		15-11-1993 25-06-1987 17-01-1985 28-03-1989 02-12-1993 14-04-1994 29-04-1994 21-09-1994 27-02-1985 10-06-1994
WO 9001323 A	22-02-1990	AU 4216089 A CA 1336762 A US 5508034 A		05-03-1990 22-08-1995 16-04-1996
JP 63277604 A	15-11-1988	NONE		
EP 0503887 A	16-09-1992	AT 141794 T AU 648877 B AU 1286192 A CA 2062653 A DE 69213057 D DE 69213057 T		15-09-1996 05-05-1994 17-09-1992 15-09-1992 02-10-1996 09-01-1997

## INTL INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 00/04696

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0503887	A	DK	503887 T	16-09-1996
		ES	2093774 T	01-01-1997
		GR	3021117 T	31-12-1996
		JP	2515458 B	10-07-1996
		JP	5070354 A	23-03-1993
		KR	221370 B	15-09-1999
		NZ	241940 A	27-07-1997
		US	5252605 A	12-10-1993
EP 0308135	A	22-03-1989	AT	72235 T
			AT	82499 T
			AT	108330 T
			AU	600168 B
			AU	2231388 A
			CA	1324129 A
			CA	1328075 A
			DE	3850676 D
			DE	3868127 A
			DE	3876050 A
			DE	3876050 T
			EP	0289349 A
			EP	0455264 A
			ES	2032016 T
			ES	2052735 T
			GB	2209939 A, B
			GR	3003749 T
			GR	3006319 T
			JP	2592204 B
			JP	6080571 A
			JP	1151552 A
			JP	1941635 C
			JP	6067900 B
			JP	1858208 C
			JP	2000108 A
			JP	5071567 B
			KR	9306202 B
			KR	9300051 B
			NZ	226197 A
			US	5001153 A
			US	5591887 A
			US	5106869 A
			US	5151444 A
			US	5770759 A
			US	5166178 A
			US	5212200 A
			US	5221763 A
			ZA	8806871 A
			ZA	8806872 A
			ZA	8806909 A
			OA	9028 A
WO 9424121	A	27-10-1994	US	5369127 A
			AT	201205 T
			AU	695059 B
			AU	1998697 A
			AU	679749 B
			AU	6770094 A
			CA	2160712 A

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal...al Application No

PCT/JP 00/04696

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9424121 A		DE 69427228 D	21-06-2001
		EP 0695300 A	07-02-1996
		ES 2156151 T	16-06-2001
		HU 73416 A	29-07-1996
		JP 8509225 T	01-10-1996
		US 5874460 A	23-02-1999
		US 5523296 A	04-06-1996
		US 5654329 A	05-08-1997
		US 5714621 A	03-02-1998
		US 5710288 A	20-01-1998
		US 5808101 A	15-09-1998
		US 5814657 A	29-09-1998